Published in final edited form as:

Schizophr Res. 2008 September ; 104(1-3): 85–95. doi:10.1016/j.schres.2008.06.013.

An fMRI study of working memory in first-degree unaffected relatives of schizophrenia patients

Shashwath A. Meda^{1,*}, Manish Bhattarai¹, Nicholas A. Morris¹, Robert S. Astur^{1,2}, Vince D. Calhoun^{1,2,3,4,5}, Daniel H. Mathalon⁶, Kent A. Kiehl^{1,2,4}, and Godfrey D. Pearlson^{1,2,3}

¹ Olin Neuropsychiatry Research Center, Institute of Living at Hartford Hospital, 200 Retreat Avenue, Hartford, CT 06106

² Dept. of Psychiatry, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510

³ Dept. of Psychiatry, Johns Hopkins University, 600 North Wolfe Street, Baltimore, MD 21287

⁴ The MIND research network, Albuquerque, NM 87131

⁵ Dept. of Electrical and Computer Engineering, University of New Mexico, Albuquerque, NM

⁶ Dept. of Psychiatry, University of California, San Francisco, CA 94143, San Francisco VA Medical Center, 4150 Clement Street, San Francisco, CA 94121

Abstract

Identifying intermediate phenotypes of genetically complex psychiatric illnesses such as schizophrenia is important. First-degree relatives of persons with schizophrenia have increased genetic risk for the disorder and tend to show deficits on working memory (WM) tasks. An open question is the relationship between such behavioral endophenotypes and the corresponding brain activation patterns revealed during functional imaging. We measured task performance during a Sternberg WM task and used functional magnetic resonance imaging (fMRI) to assess whether 23 non-affected first degree relatives showed altered performance and functional activation compared to 43 matched healthy controls. We predicted that a significant proportion of unaffected first degree relatives would show either aberrant task performance and/or abnormal related fMRI blood oxygen level dependent (BOLD) patterns. While task performance in the relatives was not different than that of controls they were significantly slower in responding to probes. Schizophrenia relatives displayed reduced activation, most markedly in bilateral dorsolateral/ventrolateral (DLPFC/VLPFC) prefrontal and posterior parietal cortex when encoding stimuli and in bilateral DLPFC and parietal areas during response selection. Additionally, fMRI differences in both conditions were modulated by load, with a parametric increase in between-group differences with load in several key regions during encoding and an opposite effect during response selection.

Keywords

fMRI; prefrontal cortex; Sternberg; working memory; schizophrenia; relatives

*Corresponding author Shashwath A. Meda, 200 Retreat Avenue, Hartford, CT 06106 USA, Tel: 860.545.7804, Fax: 860-545-7797, Email: smeda01@harthosp.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1. Introduction

Schizophrenia is a highly heritable condition, with complex genetic susceptibility likely arising from the combined effects of multiple susceptibility alleles of individually weak effect, plus environmental factors. This complicates the search for susceptibility genes with traditional linkage approaches (Gottesman 1991). An alternative approach is based on the identification of so-called intermediate phenotypes that are detectable both in patients with schizophrenia and in a higher proportion of their unaffected relatives than in the population at large (Kennedy et al., 2003; Pearlson & Folley, 2007). The advantage of such endophenotypes stems from their greater penetrance at the level of vulnerability markers, thus increasing statistical power (Cannon et al., 1993; Tsuang et al., 1993; Weinberger et al., 2001). A more recently employed strategy is thus to study unaffected first degree relatives of schizophrenia patients, who share some of the genetic diathesis without illness-related confounds (such as lower education levels or medication effects) that may themselves impact task performance.

Working memory (WM), commonly defined as the ability to hold on-line and manipulate information for short periods of time (Baddeley, 1992), has long been a central component of the study of human and animal cognition. Recent studies of WM neurocircuitry have largely focused on the prefrontal and parietal cortex, areas that has been often implicated in WM studies of nonhuman primates (Friedman & Goldman-Rakic, 1994; Petrides et al., 1995; Miller et al., 1996). Functional neuroimaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) also provide evidence for dorsolateral prefrontal cortex (DLPFC) involvement in human WM tasks (D'Esposito et al., 1999; Rypma et al., 1999; Manoach et al., 2003; Veltman et al., 2003). Nevertheless, the precise role of the DLPFC in such tasks remains to be fully elucidated.

WM tasks typically incorporate three epochs – encoding, maintenance, and response selection. Rypma and D'Esposito (1999) found DLPFC activations to be load-dependent only during encoding, suggesting that the DLPFC was primarily involved in this phase. However, using a similar task paradigm, Veltman et al., 2003 found significant load-dependent effects in bilateral middle DLPFC during response selection greater than those during encoding, concluding that the DLPFC may be involved in the response selection epoch. Also, non-human primate studies from Goldman-Rakic's lab (Friedman & Goldman-Rakic, 1994) suggest that DLPFC is involved in the maintenance phase of WM.

Considerable evidence exists suggesting that WM deficits play an important role in schizophrenia. People with schizophrenia reliably show deficits on a variety of WM tasks (Park and Holzman, 1992; Barch et al., 1998; Goldberg et al., 1998; Wexler et al., 1998; Cohen et al., 1999; Park et al., 1999). A reasonable inference from these findings is that patients' poor performance on WM tasks may be accounted for by aberrant PFC activity. This hypothesis has been confirmed by neuroimaging evidence, although the exact nature of this abnormality is under debate; earlier studies indicate patients with schizophrenia demonstrate PFC hypoactivation compared to healthy controls (Callicott et al., 1998; Yurgelun-Todd et al., 1996); while later studies demonstrate overactivation (Manoach et al., 2000; Callicott et al., 2003b). More recent WM studies have shown schizophrenia patients to have reduced activation in the DLPFC and anterior cingulate while encoding stimuli in a Sternberg task (Schlosser et al., 2008). Similarly, Koch et al., 2008 report hypoactivation of the fronto-striatal network during response selection in schizophrenia. These differences are likely dynamic and dependent both on relative task difficulty and a particular individual's baseline efficiency on a particular task, as discussed in Callicott et al., 2003b; Manoach et al., 2003 and Johnson et al., 2006. Given some of the above results from recent literature, there may be consensus that at low loads, schizophrenia patients are inefficient and over-activate, but at high loads exceeding their WM capacity they underactivate PFC.

Abnormal WM performance may be a potential endophenotype for schizophrenia based on findings of WM deficits in non-affected siblings of patients with schizophrenia (Park and Holzman, 1995; Conklin et al., 2000) and on discordant twin studies (Cannon et al., 1994; Glahn et al., 2003). In neuroimaging studies, such unaffected siblings also show aberrant PFC activation during WM tasks. In two separate cohorts, Callicott et al., 2003a found increased activation in the right DLPFC compared to healthy controls during encoding and manipulation of information, despite normal task performance. Thermenos et al., 2004, using a task combining aspects of both attention and auditory verbal working memory, showed that unaffected relatives of schizophrenia patients exhibited greater task-related activation in prefrontal cortex (DLPFC/VLPFC) and portions of thalamus; when task performance was controlled, relatives activated anterior cingulate cortex more. Brahmbhatt and colleagues (2006) show that high-risk siblings abnormally activated their PFC by demonstrating hyperactivation compared to controls during response selection to verbal stimuli. Hence, there may be utility for the use of PFC and especially DLPFC inefficiency revealed by neuroimaging, above and beyond behavioral measures of WM deficiencies, as a biomarker for schizophrenia.

Our primary objective in this study was to examine DLPFC activation of first-degree well relatives of schizophrenia patients and healthy controls during a test of WM, to assess whether or not such DLPFC activation could be employed as a schizophrenia endophenotype. Following Callicott, we specifically expected to find aberrant DLPFC activation in relatives similar to that demonstrated in schizophrenia patients. As a secondary analysis we also sought to determine if there were differences in other potential task-related regions such as VLPFC and parietal cortex.

In the present study, we employed a modified version of the Sternberg item response selection paradigm (Sternberg, 1966) and fMRI to examine task-related differences in regional brain activity in the above-described subjects. Our parametrically graded version of the Sternberg task (described in full in Johnson et al., 2006) required subjects to memorize sets of consonants of variable lengths (the target set) and then view a series of probes, deciding whether or not each probe was a member of the target set. We chose the Sternberg task instead of the *N*-back task employed by Callicott for reasons summarized in Johnson et al., 2006, including its parametric nature. Moreover, relative to the *N*-Back task, the Sternberg task allows a clearer temporal dissociation of encoding, maintenance, and response selection/response selection phases of WM. In this study, we analyzed subjects only at the medium load level (probe sizes of 4, 5 and 6; task details in the following section). We chose to analyze data at the medium level as we predicted it to be in the optimal range of task difficulty that might demonstrate maximal group differences for the cohorts being tested.

2. Methods and Materials

2.1. Subjects

We recruited 23 first-degree relatives (mean age $\pm$ SD: 46.9 $\pm$ 18.3 yrs; M: F ratio 9:14 of patients with chronic schizophrenia who were participants in an ongoing study of psychosis at the Institute of Living. Healthy controls were recruited from the hospital employee community via e-mail advertisements and “word of mouth”. The control population consisted of forty-three healthy subjects (Mean Age $\pm$ SD: 42.5 $\pm$ 20.2 yrs; M: F ratio 20:23), (See Table 1).

As seen in table 1, groups were not different on age, gender, handedness or IQ (IQ was estimated using a modified version of the National Adult Reading Test). All subjects were administered the Structured Clinical Interview for DSM-IV (SCID-IV) (First et al., 2002) to diagnose any psychotic illness. We excluded controls with a past or family history of psychosis or major mood disorder, but allowed individuals with past histories of alcohol or drug abuse. Smokers were not excluded from our study; in prior, separate work we have looked at effects of smoking

on task performance and test-related activation and found none (unpublished data). Exclusion criteria for both groups included significant medical or neurological illness at the time of participation, past major head injury, and history of alcohol or drug abuse within a 6-month period prior to participation. All subjects gave written informed consent prior to participation in the study, which was approved by the local Institutional Review Board.

2.2. fMRI Task

All subjects performed a modified version of the Sternberg task, (Johnson et al., 2006). Subjects were required to memorize a list of alphabetic consonants (encoding phase), maintain the list in memory during a delay interval (maintenance phase) and were then presented with “probe items” (response selection phase), in load sizes of 4, 5, and 6 (Medium level Sternberg task). Target letters were presented sequentially for 1.5s with a 1s inter-stimulus interval (ISI). Following the target set, there was a 9s delay before probe presentation. Probes were then presented for 2.5s with a 500ms ISI, allotting the subjects a 3s response window. Subjects had to decide if the probe was from the target set, pushing a button with the index finger of the dominant hand if the stimulus was a member of the target set or with their middle finger if it was a foil. Of the probes presented, half were part of the target set. The distribution of memory loads for the medium condition is listed in Table 2.

Before entering the MRI scanner, all subjects were given comprehensive instructions and a 7 minute practice task implemented on standard desktop PCs running custom presentation software, consisting of several iterations of each load that would be seen in-scanner. Each subject’s understanding of the task was verified by verbal confirmation as well as adequate performance on at least the lower memory loads. If necessary, practice was repeated until the subject achieved a high rate of correct responses on the easier loads.

2.3. Data Acquisition

Functional MR images were collected at the Olin Neuropsychiatry Research Center in the Institute of Living/Hartford Hospital, using a Siemens Allegra 3T scanner (Siemens, Erlangen, Germany) with a two-channel head coil. A custom head cushion was used for head stabilization and magnetic field homogeneity was handled by the scanner’s built-in shimming program. T2*-weighted images were acquired with a gradient-echo planar sequence (TR=1.86s, TE=27ms, flip=70°). The images consisted of whole-brain volumes of thirty-six sequentially acquired 3mm slices parallel to the AC-PC line (voxel size 3.44×3.44×3mm with a 1mm slice gap). Behavioral data were acquired using the visual and audio presentation package (VAPP; <http://nrc-iol.org/vapp/>)

2.4. Data Analysis

Functional images were analyzed with SPM2 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College London, UK), running in Matlab 6.5 (The Mathworks, Natick, MA) on a Solaris platform. The first five images of each time series were removed to compensate for saturation effects. Motion correction with reduced paradigm-correlation bias was achieved using INRIAlign (Freire and Mangin, 2001; Freire et al., 2002). Motion corrected images were then spatially normalized by matching them to the standardized EPI template image in SPM. After normalization, images were spatially smoothed with a 12mm isotropic Gaussian kernel and temporally filtered with a fifth-order low-pass Butterworth filter (cutoff frequency=0.25 Hz) to reduce any high-frequency noise.

As part of the first level of statistical analysis for each subject the encoding and response selection phase of the experiment were explicitly modeled as regressors of interest along with their corresponding temporal derivatives through the GLM framework in SPM. The maintenance phase was not modeled as part of the design as it was highly collinear to the other

regressors. This part of the analysis yielded the following 8 contrast images (weighted parameter estimates) for each subject: encoding_all_loads, response selection_all_loads, encoding_load_4, _load_5 and _load_6, response selection_load_4, _load_5 and _load_6. All of the above images were derived by comparing against an implicit baseline. The contrast images were then carried forward to a second level random effects (RFX) analysis to statistically compare the two groups (Healthy controls and Relatives of schizophrenia patients) using an independent sample t-tests, generating statistical group difference maps. The second level RFX analysis generated two difference images 1) Healthy Controls minus Relatives (i.e., activation significantly greater in controls than in relatives across the whole brain) and 2) Relatives minus Healthy Controls (activation significantly greater in relatives than in controls).

2.4.1. Small Volume Correction (ROI analysis)—As we had a strong region-based prediction of group differences, we chose to investigate activation differences in each of the above generated contrasts using a small volume correction (SVC) methodology in SPM2. We generated masks for the following Brodmann area(s): 7, 9, 10, 11, 44, 45 and 46, that spanned our primary regions of interest, including the entire frontal/pre-frontal cortex and the inferior and superior parietal lobes (Callicott et al., 2003; Thermenos et al., 2004; Johnson et al., 2006; Delawalla et al., 2007; Karlsgodt et al., 2007). Above ROI's were created using the WFU PickAtlas utility (http://www.fmri.wfubmc.edu/cms/software#WFU_PickAtlas). Whole brain images were initially thresholded at a $p < 0.005$ uncorrected level, then masks corresponding to the above regions were used to perform a SVC on the main effects results to investigate regions that survived for multiple comparisons (Family wise error rate or False discovery rate) within the volume of interest (Salgado-Pineda et al., 2003).

2.4.2. Whole Brain analysis—In addition to performing an ROI analysis, we also explored global differences in activation patterns across the whole brain.

3. Results

3.1. Task Performance (In-Scanner Behavioral Analysis)

Task Accuracy—Relatives' mean performance (Percentage correct mean score $\pm$ SD: 91 ± 6) was slightly lower than that of healthy controls (Percentage correct mean score $\pm$ SD: 93 ± 7), but an independent sample t-test between the two groups revealed that this difference in performance accuracy was not significant ($t(64) = 1.13$, $p = 0.26$). The scatter plot in figure 1a details individual accuracy score across the two groups.

Reaction Time—In contrast to task accuracy, the two groups differed significantly in their mean response time to correct hits and rejects ($t(64) = -3.99$; $p < 0.001$). As expected, relatives (Mean response time $\pm$ SD: 1069.72 ± 132.10 ms) had significantly longer response times than healthy controls (Mean response time $\pm$ SD: 912.66 ± 162.28 ms), as shown in figure 1b.

3.2. fMRI - Group performance

3.2.1. Small Volume Correction (ROI analysis)

3.2.1.1. Encoding Phase: Overall, when collapsed across all loads relatives significantly underactivated all ROI's except BA 11. When split across different loads, relatives BOLD responses were comparable to controls at lower loads (load 4) but demonstrated significant hypoactivations at encoding load sizes 5 and 6. Differences were observed in both dorsal and ventrolateral prefrontal cortices during both loads. However during load 5 relatives underactivated their bilateral parietal lobules to a greater extent when compared to encoding at load 6. A detailed description of all significant volumes of interest is provided in table 3 (thresholded at $p < 0.05$ FDR/FWE corrected for multiple comparisons).

3.2.1.2. Response selection Phase: Similar to encoding stimuli, relatives hypoactivated in several key regions during the response selection phase. Overall pooling across all load conditions, during response selection, relatives primarily underactivated their dorsolateral PFC and posterior parietal lobes. When investigated across different loads, interestingly relatives of schizophrenia showed significantly lower hemodynamic response amplitude during lower loads (load 4) compared to controls; however under higher loads of probe response selection there was no significant functional difference between the two groups. A detailed description of all ROI's showing group differences during response selection is provided in table 3 (thresholded at $p < 0.05$ FDR/FWE corrected for multiple comparisons).

3.2.2. Whole Brain analysis—At the whole brain level, no regions survived correction for multiple comparisons. Hence, all exploratory results are reported at the $p < 0.005$ uncorrected level.

3.2.2.1. Encoding Phase: As shown by the 2-sample t-tests (thresholded at $p < 0.005$ uncorrected), during the encoding phase, relatives in addition to under-activating the bilateral ventro/dorso-lateral PFC, and superior parietal regions, also under-activated inferior temporal regions bilaterally compared to controls. Significant regions pooled across all loads are shown in figure 2a and whole brain spatial regions color-coded by load are shown in figure 3a. No region significantly activated more in relatives than controls.

3.2.2.2. Response selection Phase: Pooled across all loads during the response selection phase, relatives under-activated their DLPFC (no VLPFC) and portions of parietal lobe more than controls, as shown in figure 2b. Figure 3b shows a main effect of group across the three different load conditions. It is interesting to note that as probe load increased group differences started to diminish, the largest group difference was seen under load 4 in multiple brain regions including the PFC (DLPFC+VLPFC), parietal cortex and inferior/middle temporal gyrus, that have often previously been implicated in schizophrenia WM deficits. As in the encoding phase, relatives showed no regional over-activation when compared to healthy controls.

4. Discussion

The pattern of fMRI task-related activations in our study generally agreed with prior studies of schizophrenia patients and their first-degree relatives (Callicott et al., 2003a,b; Manoach et al., 2003; Diwadkar et al., 2006; Brahmabhatt et al., 2007; Seidman et al., 2007; Delawalla et al., 2007; Karlsgodt et al., 2007). When we compared our results to those studies, we found that regions including left and right DLPFC (BA 9/46), inferior frontal gyrus (BA 44/45) and precentral gyrus (BA 6), consistently demonstrated aberrant functional activity in the above studies. Activation differences in middle frontal gyrus (BA 10, 11) from our study overlapped with Callicott's report and inferior parietal lobule (BA 7/40) overlapped with Manoach's results. Brain activations were also similar to those observed in our previous fMRI study (Johnson et al., 2006) that used the same task in patients with schizophrenia.

Our main findings was of reduced DLPFC and VLPFC activation in non-affected first-degree relatives compared to healthy controls during the overall encoding a phase of the Sternberg WM test (Figure 2a)., Differences during the response selection phase of the task (pooled across all loads) were more focused in bilateral DLPFC and parietal cortex., It is also notable that when pooled across all loads, activation differences in the VLPFC were minimal during response selection (See figure 2b).

When load based group differences were explored across both conditions individually, during encoding stimuli, both groups were functionally comparable under low loads (load 4), however several task related areas that are believed to support WM showed group differences at

increased loads. Comparing group differences observed under higher loads, additional left posterior parietal differences were found during load 5 compared to load 6; in contrast during load 6, group differences were more focused in the left DLPFC, i.e. as encoding load demand increased, so did differences in left DLPFC (See figure 3a). In contrast, during the response selection phase of the experiment, as load increased, group differences were less prominent across the whole brain. Marked differences were found in all of our regions of interest (except BA 46) during response selection of lower loads only (load 4); however under higher loads there were few differences in brain function between groups (See figure 3b and Table 2). Differences were found in both DLPFC and VLPFC during lower loads of this phase (Figure 3b). Similar differences particularly in the VLPFC are reported in some recent studies investigating working memory deficits in unaffected relatives of schizophrenia and first-episode schizophrenia patients (Tan et al., 2006; Schneider et al., 2007).

Behaviorally, although task accuracy was relatively unimpaired, relatives were significantly slower in reacting correctly to targets and foils presented; this might help explain some of the functional deficits and load patterns seen above.

Our findings thus offer some support for aberrant PFC activation during the Sternberg task being a potential endophenotype for schizophrenia. Additionally the pattern of activation differences seen in unaffected first-degree relatives is of great interest. Unlike Callicott et al., 2003a and Thermenos et al., 2004, who observed increased activation of DLPFC during task performance in relatives, we saw DLPFC under-activation in both the encoding and response selection phases of the task (overall and across each load).

This may be related to differences in task design and/or task difficulty, as discussed in our earlier report on fMRI activation differences in schizophrenia patients during Sternberg task performance (Johnson et al., 2006) and earlier by Callicott et al. 2003a,b, the detection of under- versus over-activation may depend on relative task difficulty for a particular individual, (as represented by an inverted U-shaped curve). This model postulates that as task difficulty increases and patients (and perhaps relatives) move from a state cognitive inefficiency and over-activation at task equi-performance, to one of cognitive failure and under-activation during task under-performance. Thus the under-activation that we observed in unaffected relatives in the face of task equi-performance (more accurately, non-significantly different under-performance), may represent a stage of early cognitive failure for this particular version of the Sternberg task. Placing our results in perspective to the above model, we found similar hypoactivation in several task related regions and especially in the DLPFC as load size increased, but this occurred only during the encoding phase of the task. Contrary to our expectation and the above postulated model, we noted an opposite effect in load modulation during response selection, where group differences diminished with increasing loads. This particular condition specific result merits further investigation to provide a more concrete conclusion. Future studies could build up on our somewhat preliminary load modulated results by including a 1. larger sample size and 2. wider spectrum of WM loads to further explore the pattern of anomalous PFC activation. It is also important to note that a potential drawback of our study is that it aims at answering a few, but not all of the major criteria needed in concretely defining an endophenotype, including whether the measure shows trait like stability over time (Gould and Gottesman, 2006).

In general, our results show anomalous, load modulated PFC activation in unaffected first-degree relatives of schizophrenia during performance of a WM task lending further support to the utility of a potentially viable imaging biomarker.

References

- Baddeley A. Working memory. *Science* 1992;255(5044):556–559. [PubMed: 1736359]
- Barch DM, Carter CS, MacDonald AW 3rd, Braver TS, Cohen JD. Context-processing deficits in schizophrenia: diagnostic specificity, 4-week course, and relationships to clinical symptoms. *J Abnorm Psychol* 2003;112(1):132–143. [PubMed: 12653421]
- Brahmbhatt SB, Haut K, Csernansky JG, Barch DM. Neural correlates of verbal and nonverbal working memory deficits in individuals with schizophrenia and their high-risk siblings. *Schizophr Res* 2006;87(1–3):191–204. [PubMed: 16842976]
- Callicott JH, Ramsey NF, Tallent K, Bertolino A, Knable MB, Coppola R, et al. Functional magnetic resonance imaging brain mapping in psychiatry: methodological issues illustrated in a study of working memory in schizophrenia. *Neuropsychopharmacology* 1998;18(3):186–196. [PubMed: 9471116]
- Callicott JH, Egan MF, Mattay VS, Bertolino A, Bone AD, Verchinski B, et al. Abnormal fMRI response of the dorsolateral prefrontal cortex in cognitively intact siblings of patients with schizophrenia. *Am J Psychiatry* 2003;160(4):709–719. [PubMed: 12668360]
- Callicott JH, Mattay VS, Verchinski BA, Marenco S, Egan MF, Weinberger DR. Complexity of prefrontal cortical dysfunction in schizophrenia: more than up or down. *Am J Psychiatry* 2003;160(12):2209–2215. [PubMed: 14638592]
- Cannon TD, van Erp TG, Glahn DC. Elucidating continuities and discontinuities between schizotypy and schizophrenia in the nervous system. *Schizophr Res* 2002;54(1–2):151–156. [PubMed: 11853989]
- Cannon TD, Rosso IM. Levels of analysis in etiological research on schizophrenia. *Dev Psychopathol* 2002;14(3):653–666. [PubMed: 12349878]
- Cohen JD, Barch DM, Carter C, Servan-Schreiber D. Context-processing deficits in schizophrenia: converging evidence from three theoretically motivated cognitive tasks. *J Abnorm Psychol* 1999;108(1):120–133. [PubMed: 10066998]
- Conklin HM, Curtis CE, Katsanis J, Iacono WG. Verbal working memory impairment in schizophrenia patients and their first-degree relatives: evidence from the digit span task. *Am J Psychiatry* 2000;157(2):275–277. [PubMed: 10671401]
- D’Esposito M, Postle BR, Ballard D, Lease J. Maintenance versus manipulation of information held in working memory: an event-related fMRI study. *Brain Cogn* 1999;41(1):66–86. [PubMed: 10536086]
- Diwadkar VA, Montrose DM, Dworakowski D, Sweeney JA, Keshavan MS. Genetically predisposed offspring with schizotypal features: an ultra high-risk group for schizophrenia? *Prog Neuropsychopharmacol Biol Psychiatry* 2006;30(2):230–238. [PubMed: 16318899]
- Freire L, Mangin JF. Motion correction algorithms may create spurious brain activations in the absence of subject motion. *Neuroimage* 2001;14(3):709–722. [PubMed: 11506543]
- Freire L, Roche A, Mangin JF. What is the best similarity measure for motion correction in fMRI time series? *IEEE Trans Med Imaging* 2002;21(5):470–484. [PubMed: 12071618]
- Friedman HR, Goldman-Rakic PS. Coactivation of prefrontal cortex and inferior parietal cortex in working memory tasks revealed by 2DG functional mapping in the rhesus monkey. *J Neurosci* 1994;14(5 Pt 1):2775–2788. [PubMed: 8182439]
- Glahn DC, Therman S, Manninen M, Huttunen M, Kaprio J, Lonnqvist J, et al. Spatial working memory as an endophenotype for schizophrenia. *Biol Psychiatry* 2003;53(7):624–626. [PubMed: 12679242]
- Goldberg TE, Patterson KJ, Taqu Y, Wilder K. Capacity limitations in short-term memory in schizophrenia: tests of competing hypotheses. *Psychol Med* 1998;28(3):665–673. [PubMed: 9626722]
- Gould TE, Gottesman II. Psychiatric endophenotypes and the development of valid animal models. *Genes Brain Behav* 2006;5(2):113–119. [PubMed: 16507002]
- Gottesman, II. *Schizophrenia Genesis: Origins of Madness*. San Francisco: WH Freeman; 1991.
- Johnson MR, Morris NA, Astur RS, Calhoun VD, Mathalon DH, Kiehl KA, et al. A functional magnetic resonance imaging study of working memory abnormalities in schizophrenia. *Biol Psychiatry* 2006;60(1):11–21. [PubMed: 16503328]
- Kennedy JL, Farrer LA, Andreasen NC, Mayeux R, St George-Hyslop P. The genetics of adult-onset neuropsychiatric disease: complexities and conundra? *Science* 2003;302(5646):822–826. [PubMed: 14593167]

- Manoach DS, Gollub RL, Benson ES, Searl MM, Goff DC, Halpern E, et al. Schizophrenic subjects show aberrant fMRI activation of dorsolateral prefrontal cortex and basal ganglia during working memory performance. *Biol Psychiatry* 2000;48(2):99–109. [PubMed: 10903406]
- Manoach DS, Greve DN, Lindgren KA, Dale AM. Identifying regional activity associated with temporally separated components of working memory using event-related functional MRI. *Neuroimage* 2003;20(3):1670–1684. [PubMed: 14642477]
- Miller EK, Erickson CA, Desimone R. Neural mechanisms of visual working memory in prefrontal cortex of the macaque. *J Neurosci* 1996;16(16):5154–5167. [PubMed: 8756444]
- Park S, Holzman PS, Lenzenweger MF. Individual differences in spatial working memory in relation to schizotypy. *J Abnorm Psychol* 1995;104(2):355–363. [PubMed: 7790637]
- Park S, Puschel J, Sauter BH, Rentsch M, Hell D. Spatial working memory deficits and clinical symptoms in schizophrenia: a 4-month follow-up study. *Biol Psychiatry* 1999;46(3):392–400. [PubMed: 10435205]
- Pearlson GD, Folley BS. Schizophrenia, Psychiatric Genetics, and Darwinian Psychiatry: An Evolutionary Framework. *Schizophr Bull.* 2007
- Pearlson GD, Folley BS. Schizophrenia, Psychiatric Genetics, and Darwinian Psychiatry: An Evolutionary Framework. *Schizophr Bull.* 2007
- Petrides M. Impairments on nonspatial self-ordered and externally ordered working memory tasks after lesions of the mid-dorsal part of the lateral frontal cortex in the monkey. *J Neurosci* 1995;15(1 Pt 1): 359–375. [PubMed: 7823141]
- Risch N. Genetic linkage and complex diseases, with special reference to psychiatric disorders. *Genet Epidemiol* 1990;7(1):3–16. [PubMed: 2184091]discussion 17–45
- Rypma B, D'Esposito M. The roles of prefrontal brain regions in components of working memory: effects of memory load and individual differences. *Proc Natl Acad Sci U S A* 1999;96(11):6558–6563. [PubMed: 10339627]
- Salgado-Pineda P, Baeza I, Perez-Gomez M, Vendrell P, Junque C, Bargallo N, et al. Sustained attention impairment correlates to gray matter decreases in first episode neuroleptic-naïve schizophrenic patients. *Neuroimage* 2003;19(2 Pt 1):365–375. [PubMed: 12814586]
- Schlosser RG, Koch K, Wagner G, Nenadic I, Roebel M, Schachtzabel C, et al. Inefficient executive cognitive control in schizophrenia is preceded by altered functional activation during information encoding: an fMRI study. *Neuropsychologia* 2008;46(1):336–347. [PubMed: 17707869]
- Schneider F, Habel U, Reske M, Kellermann T, Stocker T, Shah NJ, et al. Neural correlates of working memory dysfunction in first-episode schizophrenia patients: an fMRI multi-center study. *Schizophr Res* 2007;89(1–3):198–210. [PubMed: 17010573]
- Seidman LJ, Thermenos HW, Koch JK, Ward M, Breiter H, Goldstein JM, et al. Auditory verbal working memory load and thalamic activation in nonpsychotic relatives of persons with schizophrenia: an fMRI replication. *Neuropsychology* 2007;21(5):599–610. [PubMed: 17784808]
- Tan HY, Sust S, Buckholz JW, Mattay VS, Meyer-Lindenberg A, Egan MF, et al. Dysfunctional prefrontal regional specialization and compensation in schizophrenia. *Am J Psychiatry* 2006;163(11): 1969–1977. [PubMed: 17074949]
- Thermenos HW, Seidman LJ, Breiter H, Goldstein JM, Goodman JM, Poldrack R, et al. Functional magnetic resonance imaging during auditory verbal working memory in nonpsychotic relatives of persons with schizophrenia: a pilot study. *Biol Psychiatry* 2004;55(5):490–500. [PubMed: 15023577]
- Tsuang MT. Genotypes, phenotypes, and the brain. A search for connections in schizophrenia. *Br J Psychiatry* 1993;163:299–307. [PubMed: 8401957]
- Veltman DJ, Rombouts SA, Dolan RJ. Maintenance versus manipulation in verbal working memory revisited: an fMRI study. *Neuroimage* 2003;18(2):247–256. [PubMed: 12595179]
- Weinberger DR, Egan MF, Bertolino A, Callicott JH, Mattay VS, Lipska BK, et al. Prefrontal neurons and the genetics of schizophrenia. *Biol Psychiatry* 2001;50(11):825–844. [PubMed: 11743939]
- Wexler BE, Stevens AA, Bowers AA, Sernyak MJ, Goldman-Rakic PS. Word and tone working memory deficits in schizophrenia. *Arch Gen Psychiatry* 1998;55(12):1093–1096. [PubMed: 9862552]
- Yurgelun-Todd DA, Waternaux CM, Cohen BM, Gruber SA, English CD, Renshaw PF. Functional magnetic resonance imaging of schizophrenic patients and comparison subjects during word production. *Am J Psychiatry* 1996;153(2):200–205. [PubMed: 8561199]

Figure 1.
a, b. Scatter plot of subjects' percentage task accuracy scores (left) and reaction time in ms (right) at overall medium level of difficulty of Sternberg task.

Figure 2.

a, b. fMRI activation on 3D-rendered brain for healthy controls > relatives displayed at $p=0.005$ uncorrected level during the encoding (left) and response selection (right) phase across loads 4,5 and 6 combined.

Figure 3.

a, b. 3D fMRI activation projections for healthy controls > relatives at $p = 0.005$ uncorrected split across different load sizes for the encoding (left) and response selection (right) phases of the Sternberg task. Relatives hypo-activate their PFC during higher loads of the encoding and lower loads of the response selection phase.

Table 1

Demographic characteristics of first degree relatives and healthy controls.

Subject Characteristics	Healthy Controls (n=43) Mean $\pm$ SD	Relatives (n=23) Mean $\pm$ SD	T score	p value
Age	42.50 $\pm$ 20.2	50.80 $\pm$ 17.2	-1.54	0.12
Education (years)	11.66 $\pm$ 2.63	11.57, 2.85	0.11	0.90
Hollingshead score (Socioeconomic scale)	2.69 $\pm$ 1.51	2.75 $\pm$ 1.86	-0.08	0.93
Estimated Full-Scale IQ	103.9 $\pm$ 15.0	98.3 $\pm$ 16.5	1.31	0.19
			Chi-square	P value
Gender (M:F)	20:23	9:14	0.004	0.95
Handedness (R:L)	36:6	19:4	0.08	0.77

Table 2

Distribution of memory loads in task conditions.

Condition	Load (Letters in Memory Set)	Total Probes [*]	Targets per probe set	Occurrences of load per condition
Medium	4	4	2	3
	5	4	2	4
	6	5	2 or 3	3

* Please note: The number of probes was varied across working memory (WM) loads to achieve rough equality between the number of functional images acquired during encoding and retrieval (because the duration of the encoding period necessarily increases with growing WM load). In this way, we hoped to gain equal power to detect activation in both epochs with a fairly limited number of trials per subject.

Table 3

Small Volume (ROI) analysis on brain regions of interest during the encoding and recognition phase of the Sternberg task (Controls > Unaffected Relatives). Results are presented for both the overall load condition (i.e. across all loads collapsed) and across each load individually. Accompanying details include corresponding p-value after correcting for multiple comparisons, peak T value within the significant cluster, peak MNI coordinates and suprathreshold volume of the cluster in cm³.

	BRODMANN AREA (ROI)	REGION	ENCODING			REGION	RECOGNITION			Cluster Extent (in CC)	
			P val (FWE)	P val (FDR)	HC > REL Peak T value		P val (FWE)	P val (FDR)	HC > REL Peak T value		MNI Coords
All loads	BA 9	Middle Frontal Gyrus	0.02	0.01	3.96	-	0.04	0.05	3.67	39 51 27	1.13
	BA 10	Middle Frontal Gyrus	0.002	0.002	4.22	Superior Frontal Gyrus					
	BA 11	NS				-					
	BA 44	Inferior Frontal Gyrus	0.009	0.007	3.67						
Load 4	BA 45	Inferior Frontal Gyrus	0.04	0.01	3.25	57 12 12					
	BA 46	Middle Frontal Gyrus	0.01	0.01	3.26	60 12 21					
	BA 47	Inferior Frontal Gyrus	0.03	0.01	3.70	45 42 30					
	BA 7	Superior Parietal Lobule	NS	0.05	3.32	-42 21 -15					
	BA 40	Inferior Parietal Lobule	0.05	0.04	3.56	-15 -21 45					
	BA 9	-				54 -48 51					
	BA 10	-									
	BA 11	-									
	BA 44	-									
	BA 45	-									
Load 5	BA 46	-									
	BA 47	-									
	BA 7	-									
	BA 40	-									
	BA 9	Middle Frontal Gyrus	NS	0.04	3.65	42 6 39					
	BA 10	Superior Frontal Gyrus	NS	0.03	3.62	42 42 37					
	BA 11	NS	NS	NS	NS	NS					
	BA 44	Inferior Frontal Gyrus	0.003	0.003	4.11	57 12 12					
	BA 45	Precentral Gyrus	0.03	0.02	3.32	57 12 3					
	BA 46	Middle Frontal Gyrus	0.05	0.04	3.35	45 45 27					
Load 6	BA 47	Inferior Frontal Gyrus	0.003	0.003	4.52	36 15 -12					
	BA 7	Superior Parietal Lobule	0.007	0.005	4.32	-12 -72 45					
	BA 40	-									
	BA 9	Middle Frontal Gyrus	0.01	0.02	4.13	36 42 30					
	BA 10	Superior Frontal Gyrus	0.01	0.006	4.23	-12 57 27					
	BA 11	-									
	BA 44	Inferior Frontal Gyrus	0.03	0.03	3.22	57 15 12					
	BA 45	Inferior Frontal Gyrus	NS	0.03	3.14	60 12 21					
	BA 46	Inferior Frontal Gyrus	0.04	0.05	3.37	45 42 12					
	BA 47	-									
BA 7	-										
BA 40	-										

Schizophr Res. Author manuscript; available in PMC 2009 September 1.